FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF MILNACIPRAN HYDROCHLORIDE

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

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In

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By

Reg No: 26113306

DEPARTMENT OF PHARMACEUTICS

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OCTOBER 2013

DECLARATION

I hereby declare that this thesis work entitled **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF MILNACIPRAN HYDROCHLORIDE** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mr.K.Senthilkumar, M.Pharm, Assistant professor,** Department of pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012 - Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associate ship, fellowship of any other university or institution.

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DEDICATED TO MY PARENTS, TEACHERS AND FRIENDS

LIST OF ABBREVIATIONS

^{o}C	**:**	**Degree Centigrade**
API	**:**	**Active Pharmaceutical Ingredient**
Abs	**:**	**Absorbance**
µg/ml	**:**	**micro gram per millilitre**
λmax	**:**	**Lambda maximum**
mg	**:**	**Milligrams**
g	**:**	**Grams**
SD	**:**	**Standard deviation**
Kg/cm^2	**:**	**kilogram per centimetre square**
min	**:**	**Minute**
ml	**:**	**Milli litre**
N	**:**	**Normal**
Nm	**:**	**Nanometre**
RPM	**:**	**]rotation per minute**
Sec	**:**	**second**
Vd	**:**	**Volume of distribution**
Cm	**:**	**Centimetre**
nm	**:**	**Nanometre**
HCl	**:**	**Hydrochloric acid**
FT-IR	**:**	**Fourier Transformer Infrared**
UV	**:**	**Ultra Violet**
USP	**:**	**United States Pharmacopoeia**

INTRODUCTION

Oral route of drug administration is the most appealing route for the delivery of drugs. Oral route of drug forms administration have wide acceptance up to 50-60 % of total dosage forms[1].Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance leading to high level of patient compliance. The most popular solid dosage forms are being tablets and capsules.

Tablet is the most common and popular oral dosage form prepared and available in the market and preferred by the patients and physicians alike. Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing[2]. For any drug to exhibit its prompt pharmacological action, its serum concentration has to reach optimum level within a short period of time. Tablets constitute major portion of drug delivery systems that are currently available. However, many patient groups, such as the elderly, children and patients who are mentally retarded, non-cooperative, nauseated or on reduced liquid intake/diets have difficulties swallowing these dosage forms. Those who are travelling or have little access to water are similarly affected. To overcome these problems pharmaceutical technologists have developed a novel oral dosage form known as Oro Dispersible Tablet (ODT).

Oro dispersible tablets are those tablets which disperses upon contact with the mucosal surfaces of the oral cavity and quickly release their components without mastication or water before swallowing. Oro dispersible tablets disintegrate rapidly in saliva, usually in matter of seconds, without the need of taking water. Thus drug dissolution and absorption as well as onset of clinical effect can be obtained significantly quicker than that of conventional dosage forms. Faster the drug in solution quicker the absorption and rapid onset of action[3,4].

These tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However, of all the above terms, United States of Pharmacopoeia (USP) approved these dosage forms as ODTs (orally Pharmacopoeia disintegrating tablets). European pharmacopeia has used the term orodispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing. United States of Food and Drug Administration (FDA) defined ODT as

"A solid dosage form substance containing oractiveingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration of ODTs generally ranges from several time seconds for to about a minute[5,6].

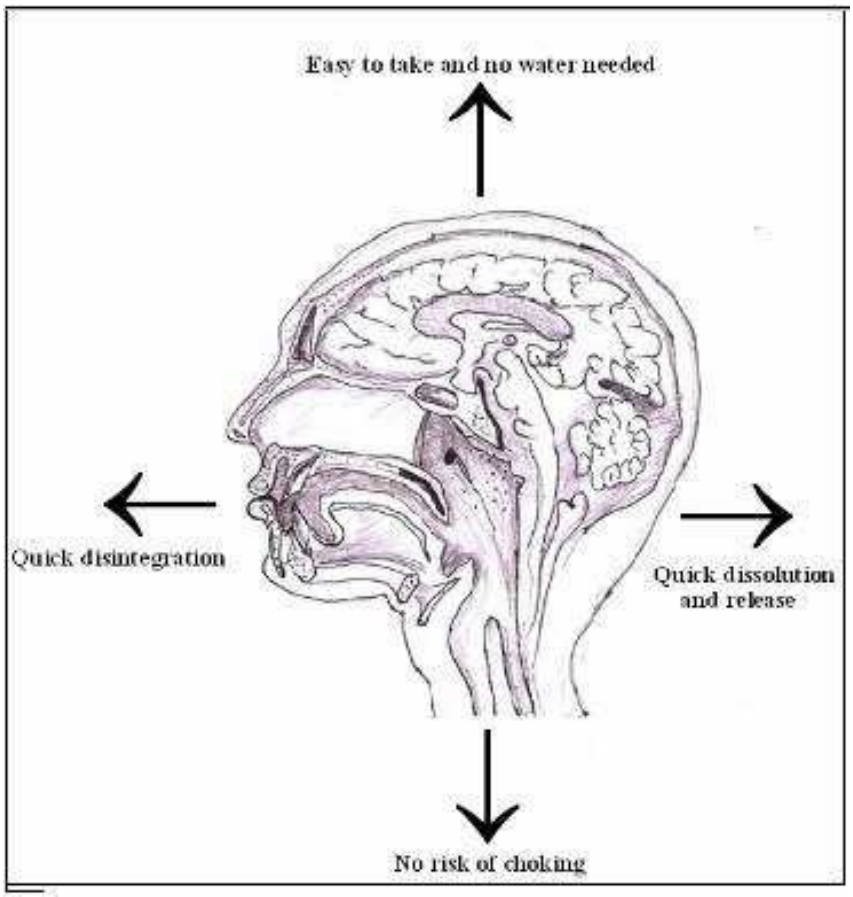


Fig.No.1.*Advantages of Orodispersible tablet*

Rapidly dissolving tablet

↓

Placed in tongue

↓

Instantaneous disintegration in the mouth

↓

Rapid drug dispersion/dissolution in saliva

↓

Pre-gastric absorption

↓

Avoid first pass metabolism

↓

Increase in bioavailability

↓

Faster onset of action

Drug selection criteria

The ideal characteristics of a drug for Oro Dispersible Tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT[7,8]

Advantages of Orodispersible Tablets

Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.

- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pre gastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- Cost effective Dosage Form
- Ideally an ODT should allow high drug loading, be compatible with taste masking and have a pleasing mouth feel and should have sufficient strength[10].

Limitations of Orodispersible tablets

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- Drugs which are relatively larger doses are difficult to formulate into ODTs.
  e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg

of the drug[10]

Need to formulate Orodispersible tablets

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. ODT is one such dosage form which is useful for Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.

- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- Especially for Patients with persistent nausea for a long period of time are unable to swallow.
- Mentally challenged patients, bedridden patients and psychiatric patients.

CHALLANGES IN FORMULATING ORODISPERSIBLE TABLETS

- **Palatability**

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

- **Mechanical strength**

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee and DuraSolv® by CIMA labs

- **Hygroscopicity**

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

- **Amount of drug**

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly important when formulating a fast-dissolving oral tablets..

- **Aqueous solubility**

Soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

- **Size of tablet**

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size is both easy to take and easy to handle is difficult to achieve

- **Mouth Feel**

Orodispersible tablets should not disintegrate into larger particle in the oral cavity. The particles generated after disintegration of orally disintegrating tablet should be small as possible.These tablets should leave minimal or no residue in mouth after oral administration.Addition of flavours and cooling agents improve the mouth feel[15,16,17].

METHODS FOR PREPARING ORODISPERSIBLE TABLETS

(a) Tablet Molding

Tablet produced by moulding are solid dispersion. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Moulding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compressing moulding). The solvent is then removed by air drying. Such tablets are less compact than compressed tablets and posses a porous structure that hastens dissolution.

The heat-moulding process involves setting the molten mass that contains a dispersed drug. The heat molding process uses an agar solution as a binder and a blister packaging well as a mould to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) pouring the suspension into the blister packaging; well solidifying the agar solution at room temperature to form a jelly and drying at 30ºC under vacuum. Moulded tablets typically do not posses great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

(b) Spray drying

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and fine powders can be produced. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and Sodium Starch Glycolate, Crosscarmellose, Crospovidone are used as a superdisintegrants. Disintegration and dissolution was further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g. sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder have been reported to disintegrate in less than 20 seconds in an aqueous medium[17].

(c) Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated

blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

(d) Freeze-Drying or Lyophillization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

(e) Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexamethelene tetramine, camphor, etc.) are added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials are then removed via sublimation, which generates porous structures. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

(f) Direct Compression

From the pharmaceutical manufacturer‟s the simplest most cost-effective tablet manufacturing procedure. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have

been widely used as bulking agents because of their high aqueous solubility, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations.

(g) Superdisintegrants addition

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are Crosscarmelose, crospovidone and sodium starch glycolate, which are a cross linked cellulose, cross-linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets.

Microcrystalline cellulose and low substituted Hydroxypropylcellulose were used as disintegrating agents in the range of 8:2 –9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch gycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants. The list of commonly used superdisintegrants with their description is shown in Table 1.1

Mechanism of Superdisintegrants:

There are four major mechanisms for tablet disintegration as follows:

1. Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

2. Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet

into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. The wicking and swelling process of disintegration is shown in Fig. 1.1.

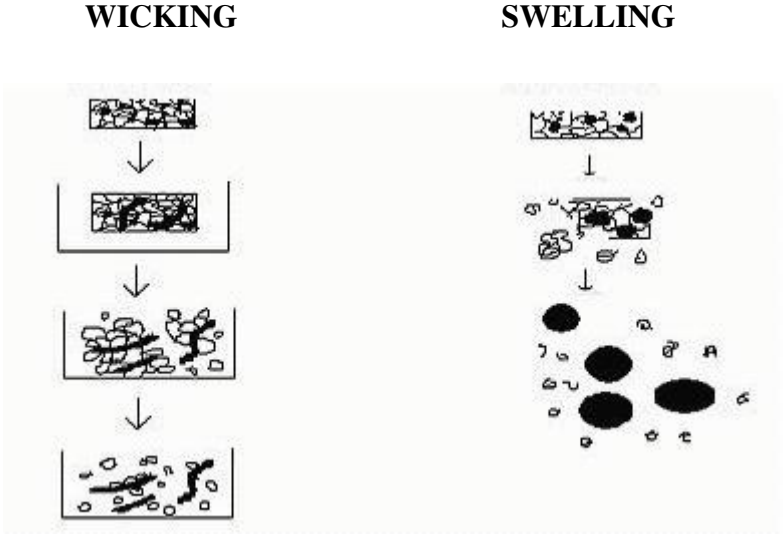


Fig.no.2. *Disintegration by wicking and swelling process*

3. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrants attempts to explain the swelling of tablet made with,, nonswellable' disintegrants. Guyot-Hermannhas proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when

granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied. Disintegration of tablets by deformation and repulsion is shown in Figure 3.

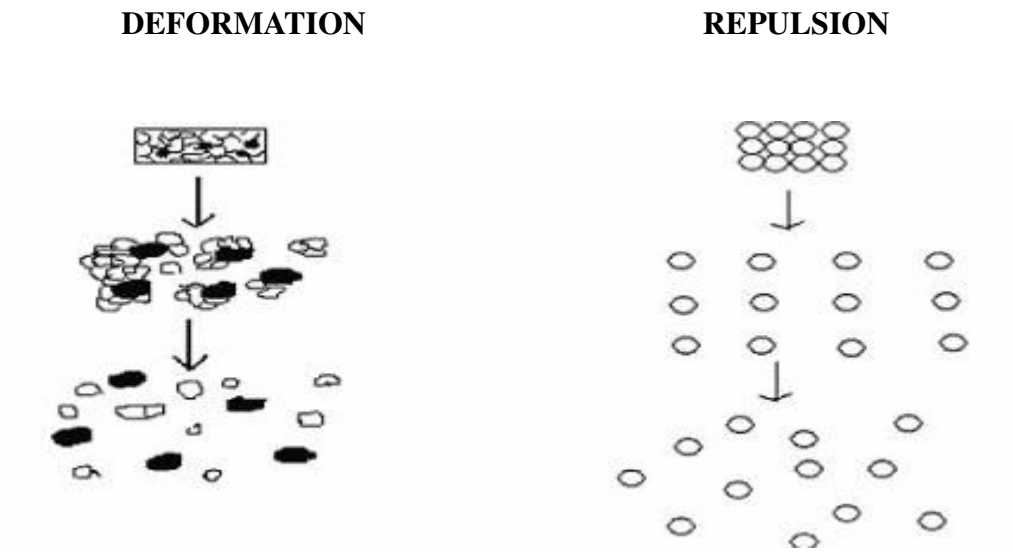


Fig.no.3. *Disintegration by deformation and repulsion process*

(h) Sugar-based Excipients

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose, isomalt and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar based materials.[12]

Table No. 1 *List of super disintegrants*

Superdisintegrants	Example	Mechanism of Action	Special comment

Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab® Vivasol®L-HPC	Crosslinked Cellulose	Swells 4-8 folds in < 10 seconds, acts by swelling And wicking both	Swells in two dimensions, used for direct compression or granulation
Crospovidone Crospovidone M® Kollidon® Polyplasdone	Crosslinked PVP	Swells very little and returns to original size after Compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch Glycolate Explotab® Primogel	Crosslinked Starch	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote Disintegration in both dry or wet Granulation
Soy polysaccharides Emcosoy®	Natural superdisintegrant		Does not contain any starch or sugar, used In nutritional products
Calcium silicate		Wicking action	Highly porous, 20- 40%

(i) Using acid treated yeast cell wall

Natural materials should be useful as pharmaceutical additives from the perspective of resource utilization and safety. Acidified brewers' yeast ce (AYC) has

been examined with respect to novel applications as it can be used as an aqueous coating material for tablets and granules. In accordance with these properties of AYC, AYC maintains the baggy structure of the original yeast. In water, AYC is dispersed as independent particles with a surface hydrogel layer. Water is included within the structure unlike other polymers.

(j) Using hydroxyl waxy binders

This work describes a new approach to prepare fast dissolving tablets with sufficient mechanical integrity, involving the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

(k) Melt granulation technique

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, apparatus of choice are the high shear mixers, where the product temperature is raised above the melting point of the binder either by a heating jacket or when the impeller speed is high enough, by the heat of friction generated by the impeller blades.

(l) Cotton candy process

The cotton candy process is also known as the candy floss process and forms the basis of the technologies such as Flash dose (Fuisz technology). An ODT is formed using a candy floss or shear from matrix and the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then partially recrystallised to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently.

(m) Suspension spray coating method

To obtain rapid disintegration granules (RDGs), a saccharide, such as trehalose, mannitol, or lactose, was spray coated with a suspension of corn starch using a fluidized-

bed granulator (suspension method). As an additional disintegrant, crospovidone, light anhydrous silicic acid or hydroxy propyl starch was also included in the suspension.[14]

PATENTED TECHNOLOGIES FOR ORODISPERSIBLE TABLETS

❖ Zydis technology

Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Thirteen products are currently available using Zydis technology. In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. On the worldwide market, other Zydis formulations are available for oxazepam, lorazepam, loperamide and enalapril.

A Zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve in the tongue in 2-3 seconds.The zydius formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. The Zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form. In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch.

❖ DuraSolv Technology

DuraSolv is Cima's second-generation fast dissolving tablet formulation. DuraSolv product is thus produced in a fashion similar to OraSolv; DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials.

The newest DuraSolv formulation, NuLev, is actually dispensed in a conventional

stock bottle. Pharmacists are advised to take care when dispensing such DuraSolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity.

❖ **OraSolv Technology**

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The Ora Solv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste-masking associated with the Ora Solv formulation is two-fold.The unpleasant flavour of a drug is not merely counteract by sweeteners or flavors; both coating the drug powder and effervescence are means of taste-masking in OraSolv. This technology is frequently used to develop over-the-counter formulations. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. The major disadvantage of the OraSolv formulations, its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets.

❖ **Flashdose technology**

Flash dose tablets consist of self-binding shear form matrix Shear form matrices are prepared by flash heat processing and are of two types:

- Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.
- Dual floss consists of a first shear f contains a carrier and at least one sugar alcohol generally sorbitol) and a second shear form binder matrix "binder floss", contains

In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid

dissolution rate of the drug. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

❖ **WOW tab technology**

WOW tab technology is patented by Yamanouchi Pharmaceutical WOW means "without water". The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, mannitol) and granulated with a high mouldability saccharide (e.g. maltose, sorbitol) and compressed into tablets. The WOWTAB product dissolves quickly in 15 seconds or less. The WOW in WOWTAB signifies the tablet is to be given without water. Two WOWTAB formulations currently on the U.S. market are Benadryl Allergy & Sinus FASTMELT and Children's Benadryl Allergy & Cold FASTMELT.

❖ **Flashtab technology**

The Flashtab technology is yet another fast dissolving/disintegrating oral tablet formulation. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute.

❖ **Frosta technology**

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 seconds depending on the size of the tablet.

❖ **LYOC Technology**

It is patented by PHARMALYOC. Oil in water emulsion is prepared and

placed directly in to blister cavities followed by freeze drying. Non- homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

❖ **QUICKSOLV technology**

This technology is patented by Janssen Pharmaceutical. It utilizes two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

❖ **AdvaTab Technology**

AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. AdvaTab is distinct from other ODT technologies as it can be combined with Eurand's complimentarytechnologieslikeits world particle leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

❖ **OraQuick technology**

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology known as Micro Mask, has superior mouth feel over taste masking alternative. The taste masking process doesnot utilize solvents of any kind and therefore leads to faster and more efficient production. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics and anti-infectives.

Advantol™ 200

Advantol™ 200 is a excipients directly system offering compressi" Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma's Advantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tableting temperature and humidity conditions to make robust-melt"let"soft.[15,17,19].

LITERATURE REVIEW

Punit.B.Parejiya *et al.,* (2011), designed the validation and development of UV spectrophotometric method for determination of UV spectrophotometric method for the determination of Milnacipran in band pharmaceutical dosage bulk and Pharmaceutical dosage form.A new,rapid and simple and sensitive spectrophotometric method has been developed for the determination of Milnacipran.The linerarity was observed in the concentration range of 2-45µg/m^{-1}.Absorbance was determined at 220nm wavelength.Results of analysis were validated statistically and by record studies.The proposed method was found accurate,reproducible and economical for the routine analysis of Milnacipran in bulk and pharmaceutical formulations[21].

Anupama Kalia A *et al*., (2009), prepared mouth dissolving tablets of oxcabazepine using two different technologies, direct compression method and solid dispersion technology. Tablets produced by direct compression method contain crospovidone as a superdisintegrant and aspartame as a sweetener. Solid dispersions of oxcarbazepine with polyvinyllpyrrolidone K-30 and polyethylene glycol 6000 in different weight ratios were prepared with a view to increase its water solubility. Oxcarbazepine solid dispersions with polyvinylpyrrolidone K-30 in 1:2 ratios of drug: carrier showed maximum drug release and hence, compressed along with other excipients into mouth dissolving tablet. The results compared for both the technologies showed that the oxcarbazepine tablets prepared using solid dispersion technology was found to have good technological properties and satisfying and reproducible drug dissolution profiles[22].

Vishal Dhiman *et.al,*.(2012),formulated and evaluated the fast dissolving tablets of Telmisartan by using Superdisintegrants such as crosscarmellose sodium,Microcrystalline cellulose and sodium starch glycolate.The tablets were prepared by direct compression method and the prepared blend were evaluated fot their physiochemical properties and in-vitro dissolution study.The evaluation studies were performed such as weight variation, thickness, Hardness, Disintegration time, Wetting time and In-vitro drug release.The disintegration time of fast dissolving tablets were increased by the addition of concentration of superdisintegrants[23].

Mihir Patel *et al*.(2012)., formulated the Olnazipane orally disintegrating tablet using Wet granulation Technique using different superdisintegrants such as SodiumStarch Glycolate,CrospovidoneXL,Crosscarmellose sodium and Kyron T-314.kyron (2%) having least disintegration time.3^2 randomized full factorial design was adopted to optimize the variable.The amount of sublimating agent,menthol and the amount of Kyron T-134 were selected as independent variables.Disintegration time and the percentage friability were selected as dependent variable.On increasing the concentration of menthol and Kyron T-134 decreases the disintegration time and shows better drug release.The stability study of selected batches were carried out at room temperature and at 40 ± 2°C/75 % BH for 3 months[24].

Sree Giri Prasad et.al(2012)., prepared and evaluated the orodispersible tablets of stavudine by direct compression technique.The purpose of this study was to optimize the formulation of Orodispersible tablets of stavudine using different superdisintegrants such as Sodium starch glycloate,Crospovidone,Crosscarmelosesodium and kollidon CLM) at different concentrations.The formulations were evaluated Tablet weight variation ,contentuniformity.hardness,friability,wetting time dispersion time,drug content and invitro release also been studied.All the formulations showed satisfactory mechanical strength and the tablet containing kollodion CLM (20%) showed excellent invitro dispersion time and drug release compared to other formulations.The results revealed that the tablets containing 20% kollidon CLM shows shorter dispersion time with maximum drug release[25].

G.Nagaprakash *et al*.,(2009) formulated rapidly disintegrating oral tablets of Valdecoxib. For formulation, they used sodium starchglycolate, crosscarmellose sodium and crospovidone as superdisintegrants and mannitol as diluent. The formulated tablets were evaluated for hardness, friability, weight variation, disintegration time and *in-vitro* dissolution studies. Finally it was concluded that the fast dissolving tablets of the poorly soluble drug can be made by direct compression technique using selective superdisintegrants[26]

Jain CP *et al*.,(2009) prepared fast dissolving tablets of Valsartan using different superdisintegrants by direct compression method, evaluated for physicochemical properties and *in vitro* dissolution. Effect of disintegrant on disintegration behavior of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing

crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing crospovidone[27]

KY Desale,**et al .,(2012)** Formulated and evaluated Fexofenadine Hydrochloride fast dissolving tablet using various Superdisintegrants by using direct compression method.In this study various range of superdisintegrants in their different concentrations were used.Superdisintegrants used were crosscarmelose sodium,crospovidone and kyron T-134. It was observed that kyron with concentration range of 1,2,3 %w/w shows drug release rate of 95.58%,96.32% and 97.46% in 20 minutes.This indicates that as the concentration increases the disintegration time also increases[28]

Parmar RB *et al*.,(2009) worked on formulation and evaluation of Domperidone fast dissolving tablets by using superdisintegrants such as Avicel PH 102 and sodium starch glycolate by direct compression.All the formulations were evaluated for characteristics such as hardness,friability,disintegration time and dissolution rate and they found a good hardness of 3kg/cm^2, disintegration time of 27 seconds and *in vitro* drug release is 95% within 30 minutes as compared to the marketed product, which gives quick release fromemesis[29]

Sanjay Modi et.al., (2012),Formulated,development and optimization of controlled porosity osmotic pump tablets of Milnacipran Hydrochloride.The CPOP tablets contains pore former,the effect of different variables like ratio of drug to osmogen .% weight gain and level of pore former in the coating solution .The in vitro drug release is studied using 2^3 factorial design.The results shows that the drug release rate increases because of the increased water uptake.Drug release was inversely proportional to membrane weight gain.[30]

Kulkarni Maushumi et.al studied on the formulation and evaluation of orodispersible tablets of ornidazole. In this, they prepared spray dried microspheres of ornidazole and formulate them into orodispersible tablets.Microsphees were formulated using polymer Polyvinyl pyrrolidone and combinations of PVP-Mannitol by spray drying technique at different ratios.The work also describes the preparation of orodispersible tablet of ornidazole by using superdisintegrants.The spray dried microspheres depicted taste masking ability,and the orodispersible tablet of ornidazole shows excellent release and

disintegration profile[31]

Parikh Bhavik et al. prepared and evaluated fast dissolving tablets of Lornoxicam fast dissolving tablet by sublimation and effervescent method using various excipients in different concentrations. crospovidone (5%) was used as superdisintegrants. The prepared formulations were evaluated for hardness, friability, disintegration time, wetting time, drug content and invitro drug release studies. Fast dissolving tablets prepared by sublimation method with 10% methanol and effervescent method with 15% sodium carbonate and 5 % citic acid showed drug release of 98.95% in 6 minutes [32].

Swamy PV *et al*., designed Orodispersible tablets of Meloxicam with a view to enhance patient compliance. A combination of superdisintegrants i.e., sodium starch glycolate-crospovidone and sodium starch glycolate-croscarmellose sodium were used with directly compressible mannitol to enhance mouth feel. Based on *in vitro* dispersion time (approximately 10 sec), two formulations (one from each batch) were tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short term stability (at 45°C for 3 weeks) and drug-excipients interaction (IR spectroscopy). Among the two formulations, the formulation containing 2% sodium starch glycolate and 1.5% crosscarmellose sodium was found to be better formulation [33].

Patel *et al*., [62] (2010), prepared mouth dissolving tablets of Diazepam using different types of superdisintegrants Ac-di-sol, sodium starch glycolate and crospovidone and different types of subliming agents camphor and ammonium bicarbonate at different concentrations and two methods of tablets preparations (wet granulation and direct compression methods). The formulations were evaluated for flow properties, wetting time, hardness, friability, content uniformity, *in vivo* disintegration time, release profiles and buccal absorption tests. All formulations showed satisfactory mechanical strength except formulation which contains camphor and formulation which was prepared by direct compression method. The results revealed that the tablets containing crospovidone as a superdisintegrant had good dissolution profile with shortest disintegration time [34].

PathikkumarJM et.al prepared orally disintegrating tablet of Dicyclomine Hydrochloride by superdisintegrant addition method .Eight formulations were prepared using Croscarmellose sodium,Sodium Starch Glycolate,Crospovidone and Indion resin -414 as superdisintegrants each in concentrations of 2% and 5%.The prepared

formulations were assessed for in process parameters and finished product parameters. Formulation with crospovidone were identified as optimized formulation amongst all the formulations developed for oral disintegrating tablets[35].

Goyani et.al.(2012),evaluated the prepared orally disintegrating tablets of Meclizine Hydrochloride using different disintegrating agents such as Sodium Starch Glycolate, croscarmellose sodium,crospovidone in different concentration by direct compression method.The formulated batches were characterized by different physical parameters.The study revealed that the formulation containing crospovidone as disintegrants shows faster disintegration compared to others[36].

Sanjay, *et al*., (2010) Fast dissolving tablets of Terbutaline sulphate were prepared using various concentration of polmers such as Microcrystalline cellulose and sodium starch glycolate, by direct compression method.. Tablets were evaluated for uniformity of weight, hardness, friability, content uniformity, wetting time, dispersion time, disintegration time and in-vitro drug release. The results were complines with the official specifications within the limits.Invitro dissolution data shows that the formulation F3 contaning sodium starch glycolate alone released 95.2 % of drug within 10 minutes [37].

Jacob, *et al*., (2007) co-processed particles of microcrystalline cellulose and mannitol were fabricated by spray drying technique to be used as direct compression excipient in fast dissolving tablet formulation. Microcrystalline cellulose passed through sieve no:80 having volumetric mean diameter (d50) of 28.35 µm was used to form composite particles with powdered mannitol which was previously passed through sieve no :80 in various mixing ratios. The composite particles were evaluated for their powder and compression properties[38].

Abdul Jaleel *et al*., (**2010**) The research was to enhance the dissolution of orally disintegrated tablets of loratadine. Orodispersible tablets of loratadine were prepared using different types and concentrations of superdisintegrant (Ac-Di-Sol, sodium starch glycolate, and crospovidone (CP)) using direct compression method. The drug is poorly water soluble therefore to enhance the solubility and release of drug, solid dispersion of drug with PVP K30 was prepared by solvent evaporation method. The formulas were evaluated for flow properties, wetting time, hardness, friability, content uniformity, in

vivo disintegration time (DT), release profiles, and buccal absorption tests. All formulations showed satisfactory mechanical strength and friability. The results revealed that the tablets containing CP as a superdisintegrant have good dissolution profile with shortest DT[39].

V.Anand et.al**(2007)** prepared taste-masked orally disintegrating tablets of Prednisolone by incorporation of microspheres in the tablets by solvent evaporation method..Tablets were prepared by direct compression method containing microspheres,were evaluated with regrad to crushing strength,friability,disintegration time ,drug content and in vitro drug release and .taste evaluation studies confirmed that micospheres of PDL having a drug to polymer ratio 1.10 are tasteless and these wee further used for formulation in ODTs.Effective taste masking was achieved for PDL using the technique of microencapsulation and ODTs of acceptable characteristics were obtained by disintegrationaddition and direct compression method[40].

Garg Ashish et.al(2013) Taste masking and formulation and evaluation of mouth dissolving tablets of Levocetrizine dihydrochloride.Results shows that effective taste masking is achieved for Levocetrizine hydrochloride by preparing drug resin complex using Kyron T-134 The tablets are evaluated for the drug content,weight variation, and water absorption ratio,wetting time,invitro disintegration ,hardness,friability,thickness uniformity and in-vitro dissolution[41].

Suresh vk et al.(2010) studied the effect of superdisintegrant on the formulation of taste masked fast disintegrating Lisnopril Tablets.superdisintegrants such as crospovidone crosscarmellose sodium were used..Tablets were evaluated for the weight variation ,thickness,disintegration time ,dissolution time. Tablets containing crospovidone exhibit quick disintegration time than tablets containing croscarmellosesodium[42]

SCOPE OF WORK

Antidepressant is a Psychiatric medication used for alleviating major depression. Depression is a state of low mood and aversion to activity that can affect a person's thought, behaviour feelings and sense of well being. The major cause of depression is an inadequate amount of serotonin and altering levels of neurotransmitters.

Milnacipran Hydrochloride is a potential fourth generation antidepressant drug .It is a selective norepinerphine serotonin reuptake inhibitor.It inhibit nor epinerphine uptake with greater potency than serotonin.

Milnacipran Hydrochloride is indicated for the treatment of major depressive disorder.In January 2009,approved FDA Milnacipran Hydrochloride (under the brand name Savella) only for the treatment of fibromyalagia, making it is the third medication approved for this purpose in the united states. Milnacipran Hydrochloride is available as conventional dosage forms such as tablets (12.5, 25, 50 and 100 mg) and as capsules (25, 50 and 100 mg). Milnacipran Hydrochloride is available in India as tablets and capsules from leading pharmaceutical companies such as Ranbaxy, Intas, Torrent, and Sun pharma But Milnacipran Hydrochloride is not available as orally disintegrating tablet in India as well as in US market.

In case of major depressive disorders and in fibromyalgia, patients having jaw and facial tenderness, impared concentration, troubled in thinking, difficulty in remembering.The treatment of above mentioned condition requires continuous drug therapy and patient compliance.

In order to treat the disease effectively and to improve the patient complaince, the Milnacipran Hydrochloride was planned to prepare as an orodispersible tablets. These tablets disintegrates quickly in the saliva (without the need of water), within a matter of seconds in oral cavity. Thus it helps to achieve rapid onset of action and improves patient compliance. These are all the salient features of selecting Milnacipran Hydrochloride as an orodispersible tablets.

OBJECTIVE

The main objective of present work is to prepare the orally disintegrating tablets of Milnacipran Hydrochloride using different super disintegrants.

PLAN OF WORK

PREFORMULATION STUDY

Organoleptic evaluation of API

Analytical Evaluation of API

- FTIR spectroscopic Analysis
- UV spectroscopic Analysis

Formulation Development

- Selection of Excipients
- Preparation of blend
- Direct compression of orally Disintegrating Tablets
- Evaluation of blend for bulk characterisation

Evaluation of formulation

- Weight variation
- Thickness
- Crushing Strength
- Friability
- Disintegration Time
- Dispersion time
- Water absorption ratio
- Wetting time
- Drug Content
- Uniformity of Dosage forms
- *Invitro* Dissolution study

MATERIALS AND INSTRUMENTS USED

All the chemicals and other materials used in the present investigation were the best grade available in the laboratory and supplied by the manufactures.

Table .No.2 List of Materials Used

Raw materials	Source
Milnacipran Hydrochloride	Par Parmaceuticals, Chennai.
Mannitol (Pearlitol SD 200)	Par Pharmaceuticals , Chennai.
Kyron T-314 (Pollacrillin Potassium)	Corel Pharma Chem, Ahmedabad.
Crosscarmellose sodium	Par Pharmaceutical, Chennai.
Sodium Starch Glycolate	Par Pharmaceuticals, Chennai.
Crospovidone	Par Pharmaceuticals, Chennai.
Aerosil 200 (Collodial Silicon Dioxide)	Merck Specialities Private limited. Mumbai
Povidone	Par Pharmaceuticals ,Chennai.
Magnesium Stearate	Vama Pharma, Nagpur.
Sucralose	SD fine chem, Mumbai
Vanilla flavour	SD fine chem, Mumbai

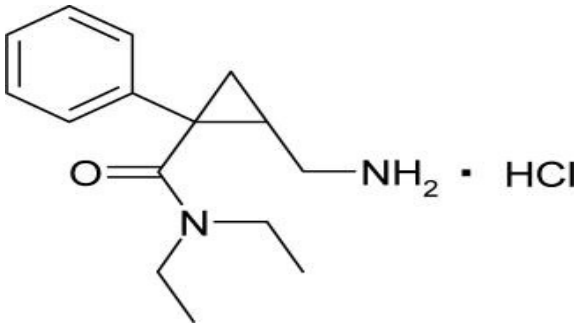
Table .No.3 list of equipments used

Instruments	**Suppliers**
Electronic Weighing Balance	Shimadzu philippines manufacturing, Japan(243IZ)
Tablet compression machine	Cemach machineries LTD ,Ahamedabad
Vernier Caliper	Mitutoyo,Absolute,Digimatic
Tablet Hardness tester	Praveen enterprises
Friability test apparatus	PSM industries, Mumbai
Sieves	Jayanath Test Sieves
Dissolution test apparatus (disso2000)(USP)	Labindia instruments PVT LTD,Mumbai
UV-Visible spectrophotometer	Systronic 118
T.A.X.T plus Texture Analyser	Stable Micro System,U.K
Disintegration tester USP	Electrolab Mod
Dissolution Apparatus	USP-2-DS-8000 Manufactured by Electrolab, Mumbai
FTIR spectrophotometer	Perkin- Elmer Lambda 40P

DRUG PROFILE[43,44,45]

Drug Name	:	Milnacipran Hydrochloride
Chemical Name	:	(±)-[1R(s),2s(R)]-2-(amino methyl)-N,N-diethyl-phenylcyclopropane carboxamide hydrochloride.
Molecular Formula	:	$C_{15}H_{22}N_{20}$.HCl
Molecular Weight	:	282.81
CAS Register Number	:	101152-94-7
Category	;	Major depressive disorder Management of fibromyalagia
Descripition	:	White to off white crystalline powder
Solubility	:	freely soluable inwater,methanol,ethanol,chloroform and methylchloride. Sparingly soluable in diethylether
BCS Class	:	Class I (Highly Soluable.Highly Permeable)
Melting Point	:	179°C
Storage	:	Store at tightly closed container,protected from moisture.
PKa Value	:	9.83
Dose	:	Initial dose on day 1 – 12.5 mg Day 2 and 3 – 12.5 mg twice daily Day 4 through 7 - 25 mg twice daily After day 7 - 50 mg twice daily

Structural Formula



Clinical pharmacology

Mechanism

The exact mechanism of the central pain inhibitory action of Milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown. Preclinical studies have shown that Milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake; Milnacipran inhibits norepinephrine uptake with approximately 3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or other neurotransmitters. Milnacipran has no significant affinity for serotonergic (5-HT1-7), α- and β-adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazepine, and γ-aminobutyric acid (GABA) receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Milnacipran has no significant affinity for Ca^{++}, K^{+}, Na^{+} and Cl^{-} channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.

Pharmacokinetics

Milnacipran is well absorbed after oral administration with an absolute bioavailability of approximately 85% to 90%. The exposure to milnacipran increased proportionally within the therapeutic dose range. It is excreted predominantly unchanged in urine (55%) and has a terminal elimination half-life of about 6 to 8 hours. Steady-state levels are reached within 36 to 48 hours and can be predicted from single-dose data. The active enantiomer, d-milnacipran, has a longer elimination half-life (8-10 hours) than the l-enantiomer (4-6 hours). There is no interconversion between the enantiomers.

Absorption and Distribution

Milnacipran is absorbed following oral administration with maximum concentrations (Cmax) reached within 2 to 4 hours post dose. Absorption of the drug is not affected by food. The absolute bioavailability is approximately 85% to 90%. The mean volume of distribution of Milnacipran following a single intravenous dose to healthy subjects is approximately 400 L.

Plasma protein binding is 13%.

Metabolism and Elimination

Hepatic metabolism of Milnacipran occurs via glucuronidation. No involvement of CYP450 isozymes or active metabolites found.

Milnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of ^{14}C-milnacipran hydrochloride, approximately 55% of the dose was excreted in urine as unchanged Milnacipran (24% as l-Milnacipran and 31% as d-Milnacipran). The l-Milnacipran carbamoyl-O-glucuronide was the major metabolite excreted in urine and accounted for approximately 17% of the dose; approximately 2% of the dose was excreted in urine as d-Milnacipran carbamoyl-O-glucuronide. Approximately 8% of the dose was excreted in urine as the N-desethyl Milnacipran metabolite.

Toxicity Data

LD50, oral, rat: 213 mg/kg. The most frequently occurring adverse reactions (≥ 5% and greater than placebo) were nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension.

Half Life

The terminal elimination half-life, when given to healthy subjects is 6-8 hours. When given to severe renal impairment patients is 7 - 10 hours. The active enantiomer, d-Milnacipran, has a longer elimination half-life (8-10 hours) than the l-enantiomer (4-6 hours).

Therapeutic Indications

Milnacipran Hydrochloride is used in major depressive disorder and in fibromyalagia.

Contraindications

Contraindicated in patients with known hypersensitivity to Milnacipran, during lactaction, pregnancy,and in prostatic hypertrophy and in genitor-urinary disorders. milnacipran hydrochloride is also contraindicated on association with non-selective MAO inhibitors, digitalis and with 5HT agonists.

Interactions

Milnacipran Hydrochloride with 5-HT receptor agonists causes coronary vasoconstriction with risk of angina pectoris and myocardial infaraction,with Epinephrine,Norepinephrine hypertensive possible cardiac arrthymia may occur. Milnacipran Hydrochloride antagonises the hypertensive action of clonidine.With Digitalis,Milnacipran hydrochloride increases the hemodynamic actions.

Adverse Effects[39,40]

Adverse effects include Nausea, vomiting, Dry mouth, Constipation. Loss of appetie, Dizziness, Increased sweating, Headache, Hot flashrs, palpitations, migrane, tachycardia

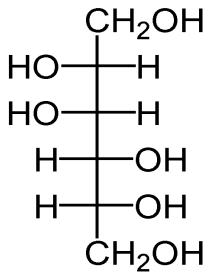
EXCIPENT PROFILE

MANNITOL[46]

Synonyms:

Cordycepic acid, manna sugar, D-mannite, mannite

Chemical Structure:



Description:

- Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.
- Mannitol occurs as a white, odorless, crystalline powder or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

Chemical Name **:** D - Mannitol

Empirical Formula **:** $C_6 H_{14} O_6$

Molecular Weight **:** 182.17

Functional Category:

Sweetening agent, tablet and capsule diluents, tonicity agent, vehicle (bulking agent) for lyophilized preparations.

Application in Pharmaceutical Formulation:

Mannitol is widely used in pharmaceutical formulations and food products.

- In pharmaceutical preparations it is primarily used as a diluents (10-90% w/w) in tablet formulations.
- Mannitol is commonly used as an excipient in the manufactures of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Stability and Storage Condition:

Mannitol is stable in the dry state and in aqueous solutions. In solution, mannitol is not attacked by cold, dilute acids or alkalis, not by atmospheric oxygen in the absence of catalysts.

Incompatibilities:

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.

Safety:

After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the rental tubule, about 80% of a dosage being excreted in the urine in 3 hours..[22]

CROSS CARMELLOSE SODIUM[46]

Non proprietary names:

BP : cross caramelise sodium

Ph EUR : carmellose natricum conexum

USP NF : cross caramelise sodium

Synonym:

A cross-linked polymer of Carboxymethylcellulose sodium; Ac-Di-Sol; Explocel

Chemical Name ***and CAS registry number****:*

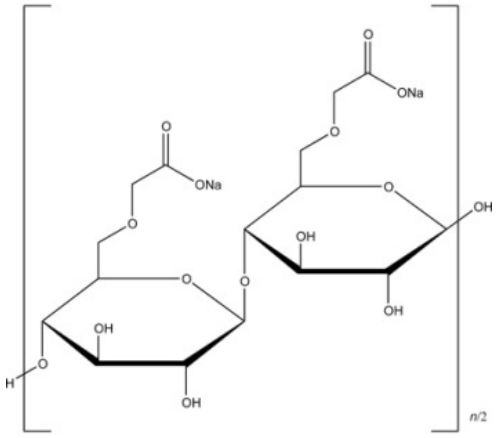
Cellulose, carboxymethyl ether, sodium salt, cross linked [74811-65-7]

Empirical formula molecular weight:

Crosscarmellose sodium is a cross linked polymer of carboxyl methyl cellulose sodium.

Molecular Weight: 570.49 gm

Structural formula:



Description:

Crosscarmollese sodium occurs as an order less, white or grayish white powder. Crosscarmellose sodium is a cross linked polymer of carboxy methyl cellulose sodium. Crosslinking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities. Crosscarmellose sodium provides superior drug dissolution and disintegration characteristics, thus improving bioavailability of formulations

Functional Category:

Use as a superdisintegrant in pharmaceutical formulations

Stability and storage conditions :

Crosscarmellose sodium is a stable though hygroscopic material. It should be stored in a well-closed container in a cool, dry, place

CROSPOVIDONE[39]

Non proprietary names:

BP : povidone

JP : povidone

Pheur : povi done

USP : povidone

Synonyms:

Crosspovidone, Crosspovidonum, Insolublepolyvinylpyrrolidine, Crosslinkedpvp, kollidone

Description:

Crospovidone is a water-insoluble synthetic cross-linked homo- polymer of *N*-vinyl-2-pyrrolidinone. It contains NLT 11.0% and NMT 12.8% of nitrogen (N), calculated on the anhydrous basis.

Chemical name:

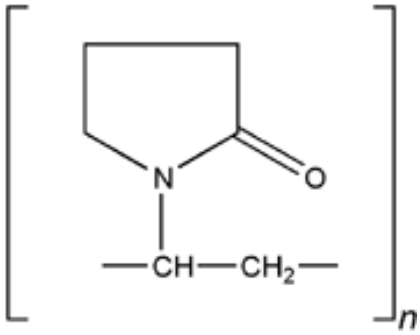
1-Ethenyl-2-pyrrolidinone homopolymer

1-Vinyl-2-pyrrolidinone homopolymer

Empirical Formula and molecular weight:

(C6H9NO)*n,* 2500-3,000000

Structural formula:



Functional category:

Used as superdisintegrant dissolution aid, suspending agent, tablet binder*, in* pharmaceutical formulations.

Applications in pharmaceutical formulation or technology:

Although crospovidone is used in a variety of pharmaceutical formulations ,it is primarily used in solid-dosage forms in tableting , Povidone solutions are used as binders in wet-granulation process. Poll done is also added to powder blends in the dry form and granulated in situ by the addition of water , alcohol ,or hydro alcoholic solutions , povidone is used as a solubilizer in oral and parentral formulation and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Poll done solution may also be used in coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity .increasing agent in number of topical agents

Typical Properties:

Acidity/alkalinity; PH=8.0-7.0(8% w/v aqueous solution)

Density (bulk):0.29-0.39 g/cm^3 for povidone

Density (tapped):0.39-0.54 g/cm^3 for povidone

Density (true): 1.180 g/cm3

Flowability:

20 g/s for povidone k-15

16 g/s for povidone k-29/32

Melting point: soften at 150^{0}C

Moisture contents:

Povidone is very hygrosopic significant amount of moisture seing absorbed at low relative humidities.

Solubility:

Freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarsons, and mineral oil.

In water the concentration of a solution is limited only by the viscosity of the solution, which is a function of the k-value.

Stability and storage conditions:

Povidone darkens to some extent on heating at 150°C , with a reduction in aqueous solubility .it is stable to short cycle of heat exposure around 110-130°C; steam sterilization of an aqueous solution does not after its properties .aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cold dry place[22,23]

KYRON T -134[46] **(Polacrillin potassium)**

Nonproprietary Names USPNF : Polacirilin potassium

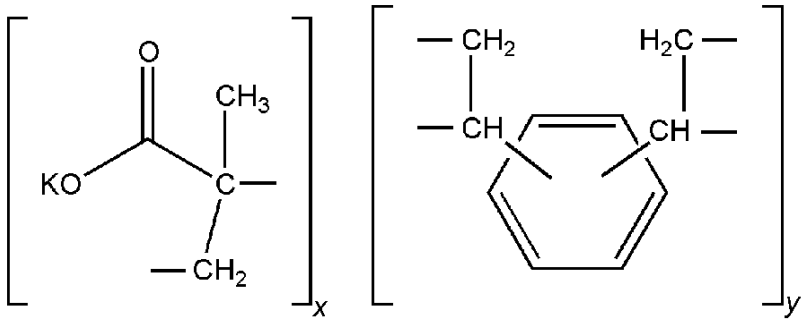
Synonyms:

Amberlite IRP-88; methacrylic acid polymer with divinylben- zene, potassium salt; polacrilinum kalii.

Chemical Name and CAS Registry Number

2-Methyl-2-propenoic acid polymer with divinylbenzene, potassium salt [39394-76-5]

Structural Formula



Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Polacrilin potassium is a cation-exchange resin used in oral pharmaceutical formulations as a tablet disintegrant.(1–3%) Concentrations of 2–10% w/w have been used for this purpose although 2% w/w of polacrilin potassium is usually sufficient. Other polacrilin ion-exchange resins have been used as excipients to stabilize drugs, to mask or modify the taste of drugs, and in the preparation of sustained-release dosage forms and drug carriers.

Polacrilin resins are also used in the analysis and manufacture of pharmaceuticals and food products.

Description

Polacrilin potassium occurs as a cream-colored, odorless and tasteless, free-flowing powder. Aqueous dispersions have a bitter taste.

Typical Properties

Density(bulk) :0.48 g/cm^2 for Amberlite IRP-88

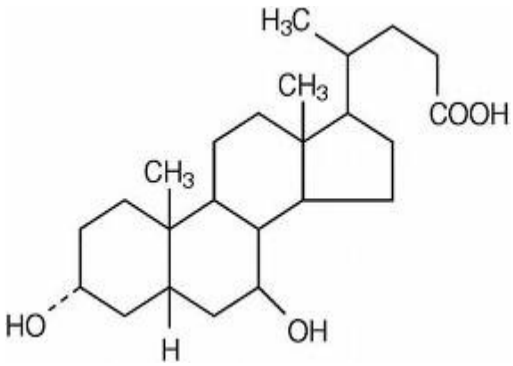
Density(tapped) : 0.62 g/cm^2 for Amberlite IRP-88

Solubility : practically insoluable in water and most other liquids, although polacrilin resins swell rapidly when wetted.

SODIUM STARCH GLYCOLATE[46,47]

Synonyms: Explotab, Primogel.

Structural formula:



Non-proprietary Name:

BP-Sodium starch glycolate,

USPNF-Sodium starch glycolate

Functional category **:** Tablet and capsule disintegrant.

Chemical names **:** Sodium carboxymethyl starch.

Solubility **:** Practically insoluble in water, sparingly soluble in ethanol

Incompatibilities **:** Incompatible with ascorbic acid.

Description:

Sodium starch glycolate is a white to off-white, odourless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 μm in diamet some less spherical granules ranging from 10-35 μm in diameter.

Stability and storage conditions:

It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Safet:

It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications:

As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

Stability and Storage conditions:

Polacirillin potassium and other polacrilin resins are stable to light ,air and heat up to their maximum temperature Excessive bledding can cause thermal decomposition of the resins and yield one or more oxides of carbon,Nitrogen,sulfer and or amines

POVIDONE[46]

Nonproprietary Names

BP : Povidone

JP : Povidone

PhEur : Povidonum

USP : Povidone

Synonyms

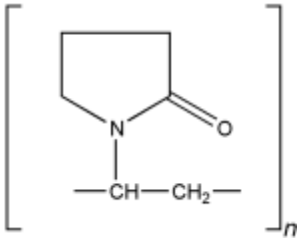
poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula

$(C_6H_9NO)_n$



Functional Category

Disintegrant, dissolution aid, suspending agent and tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, Povidone is used as binders in wet-granulation processes and as coating agents.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder and freely soluble in acids, chloroform, methanol, and water practically insoluble in ether, hydrocarbons and mineral oil.

Stability and Storage Conditions

The powder is hygroscopic; it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

Safety

Povidone may be regarded as nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.

COLLOIDAL SILICON DIOXIDE (AEROSIL)[46]

Synonyms

Aerosil, Cab-O-Sil, colloidal silica, light anhydrous silicic acid, silicic anhydride, Silicon dioxide fumed.

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15nm.It is a light, loose, bluish-white-colored, odorless, tasteless, non-gritty amorphous powder.

Chemical Name : Silica

Empirical Formula : SiO_2

Molecular Weight : 60.08

Functional Category : Adsorbent, anti caking agent, glidant, tablet Disintegrant, viscosity-increasing agent.

Application in Pharmaceutical Formulation:

- Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products.
- Colloidal silicon dioxide is also used to stabilize emulsions and as a thyrotrophic thickening and suspending agent in gels and semisolid preparations.
- Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent, dispersing agent for liquids in powders.

Stability and Storage Condition:

- Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying.
- Colloidal silicon dioxide powder should be stored in well-closed container.

Incompatibilities: Incompatible with diethylstilboestrol preparations.

Safety: Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially non-toxic and non-irritant excipients

MAGNESIUM STEARATE[46]

Nonproprietary Names

BP : Magnesium stearate

JP : Magnesium stearate

PhEur : Magnesii stearate

USPNF : Magnesium stearate

Synonyms

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name

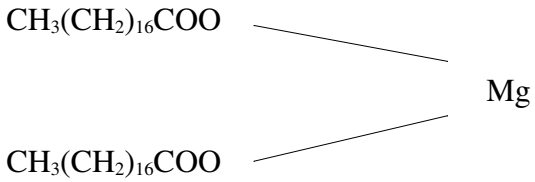
Octadecanoic acid magnesium salt

CAS Register Number : [557-04-0]

Empirical Formula

$C_{36}H_{70}MgO_4$

Structural Formula



Molecular Weight : 591.34

Functional Category

Tablet lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used as a lubricant.

Description

It is a very fine, light white, precipitated powder of low bulk density, having a faint odor of stearic acid with a characteristic taste and greasy to the touch and readily adheres to the skin. Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene.

Typical properties

Density (bulk)	: 0.519 g/cm^3
Density (tapped)	: 0.289 g/cm^3
Density (true)	: 1.092 g/cm^2
Flash point	: 250°C
Flowability	: poorly flowing,cohesive powder
Melting range	:117-150°C (commercial samples)
	126-130°C (high purity magnesium strearate)
Solubility	: practically insoluable in ethanol,ether and water,slightly
	soluable in warm benzene and warm water
Specific surface area	:1.6 – 14.8 m^2/g

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with strong acids, alkalis, iron salts and strong oxidizing materials.

Safety

Magnesium Streate has not been shown to be carcinogenic when implanted into the bladder of mice.LD_{50} (rat,inhalation) : > 2mg/L

LD_{50} (rat,oral) : > 10 g/kg

SUCRALOSE[46]

Non proprietary Names: USPNF: Sucralose

Synonyms:

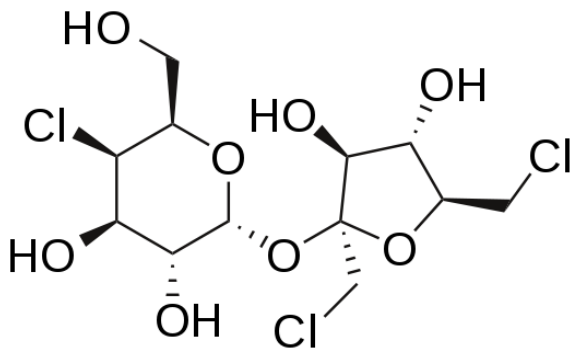
Splenda;sucralosa;sucralosum;SucraPlus

Chemical Name

1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α D-galactopyranoside -E955, Trichlorosucrose

CAS Registry Number :[56038-13-2]

Structural formula:



Empirical Formula : $C_{12}H_{19}Cl_3O_8$

Molecular Weight : 397.63

Functional Category :

Use as a sweetner in pharmaceutical formulation

Applications in pharmaceutical formulation or Technology

Sucralose is used as a sweeting agent in beverages,foods,and Pharmaceutical applications.I has a sweetening power approximately 300-1000 times that of sucrose and no aftertaste.In food products Sucralose used in concentration of 0.03- 0.2%.

Description

It is a white to off-white colour, free –flowing,crystalline powder.

Typical Properties

Density (bulk) : 0.35 g/cm^2

Density (tapped) : 0.62 g/cm^2

Melting point : 130 °C (for anhydrous crystalline form)

: 36.58°C (for pentahydrate)

Solubility : freely soluable in ethanol,methanol and water,slightly soluable in ethyl acetate.

Stability and Storage Conditions

Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3),and at high temperatures (35°C),it is hydrolyzed to limited extend ,producing 4-chloro-4 deoxygalactose and 1,6- dichloro-1,6 –dideoxyfructose.Sucralose should be stored in a well- closed container in a cool,dry place,at a temperature not exceeding 21°C.

EXPERIMENTAL WORK

Preformulation Studies

Preformulation is the first step in the formulation studies.It includes the application of biopharmaceutical principles to the physiochemical properties of a drug with the goal of designing an optimum drug delivery system which is stable,bioavaliable and can be mass-produced[2].

❖ **Organoleptic Evaluation**

Organoleptic characters of drug was observed and recorded by using descriptive terminology.Following physical properties of API were studied.

- Color
- Odor
- Taste

❖ **Analytical Evaluation**

- IR Spectroscopic Analysis
- UV Spectroscopical Analysis

- ***IR Spectroscopic Analysis***

Milnacipran Hydrochloride, placebo and final lubricated blend of orally disintegrating tablets were analyzed by Infra Red spectroscopy (FTIR 8400S) by KBr pellet method.They are compressed under high pressure in a hydraulic press to form a transperant pellet.The pellet was scanned from 4000cm^{-1} to 400cm^{-1} in FTIR.The change in the obtained peaks of pure drug,excipients were compared with drug-excipients mixture.

Determination of λ_{max} of selected candidate.

Preparation of medium (0.1N Hydrochloric acid)

8.5 ml of hydrochloric acid was diluted with distilled water and volume made upto 1000 ml

Procedure for the determination of λ_{max}

A solution of Milnacipran Hydrohloride a containing conc. 10µg/ml was prepared in 0.1 N Hydrochloric acid and UV spectrum was taken using Systronic 118 (UV-1800)

spectrophotometer. The solution was scanned in the range of 200-400nm.

- ***UV spectroscopic Analysis***

Preparation of Calibration Curve of Milnacipran Hydrochloride[32,52]

For preparation of the stock, the drug Milnacipran Hydrochloride (100 mg) was dissolved in 100 ml of 0.1N Hydrochloride to obtain a stock solution (1000 µg).10 ml of solution was taken and further diluted to 100 ml. The obtained solution of Milnacipran Hydrochloride (100 µg/ml) was used as standard stock solution.

From the stock solution 5,10,15,20,25,and 30 µg/ml. Absorbance of each solution was measured at 223 nm using UV / Visible spectrophotometer.

The following studies were done for Milnacipran Hydrochloride and for all the formulations.

a) Bulk Density (Db)[53]

It is the ratio of total mass of powder to the bulk volume of powder.It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the intial volume was noted.This initial volume is called the bulk volume.From this, the bulk density is calculated according to formula mentioned below.it is expressed in g/ml and is given by

$D_b = M / V_o$

M - The mass of powder

V_o - The bulk volume of powder (ml)

b) Tapped Density[53]

It is the ratio of total mass of powder to the tapped volume of powder.Volume was measured by tapping the powder for 500, 750 times and the tapped volume was noted. if the difference between these two volumes is less than 2% the volume was taken as

tapped volume.If it is more than 2% tapping is continued for 1250 times and tapped volume was noted.Tapping was continued until the difference between successive volumes is less than 2%.It is expressed in g/ml and is given by

$$D_t = M / V_f$$

Where,

M – The mass of powder

V_f – The tapped volume of the powder.

C) Compressibility Index[53] (Carr's Index)

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations.It is one of the simple method to evaluate the flow property of powder by comparing the bulk density and tapped density.

Carr' s index= $100(V_o - V_f) / V_o$

TableNo: 4 Relationship between % Compressibility and Flowability

% Compressibility	Flow character
5 –12	Excellent
12 –16	Good
18 –21	Fair Passable
23 –35	Poor
33 –38	Very Poor
< 40	Very Very Poor

D) Hausner's ratio[53]

It is an indication of degree of densification.The hausner ratio of the powder was determined by the following equation

Hausner's ratio = V_o/V_f

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose[53] ( )

The frictional force in a loose powder or granules can be measured by angle of repose.

Angle of repose is the maximum angle between the surface of a pile of powder and horizontal plane,It is usually determined by fixed funnel method suggested by Newmann and is the measure of flow ability of powder / granules.

A funnel with 10 mm inner diameter of stem was fixed at a height of 6 cm,over the platform.About 25 gm of sample was slowly passed along the wall of the funnel till of the pile formed and touches the stem of the funnel,A rough circle was drawn around the pile base and the radius of the powder cone was measured.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

TableNo. 5 Angle of repose as an indication of powder flow properties

Angle of repose	Flow
¿ 25	Excellent
20-30	Good
30-40	Passable
¿ 40	Very poor

Formulation Development

In this work, direct compression method with the aid of superdisintegrants was attempted for the formulation development of rapid dissolving tablets of Milnacipran Hydrochloride. 12.5 mg of Milnacipran Hydrochloride was selected for the present study with an average weight of 100mg tablet.

Development of the formulation in the present study was mainly based on the type and concentration of superdisintegrant and the properties of the drug. Various superdisintegrant in different concentrations (3% and 5%) were used so as to get tablets with good physical properties. The formulation design of rapid dissolving tablets of Milnacipran Hydrochloride is shown in Table

Table no.6 Formulation design of Milnacipran Hydrochloride Orally dissolving tablets

	mg/tab						
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**

Milnacipran Hydrochloride	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mannitol (Pearlitol SD200)	70.5	70.5	70.5	70.5	72.5	72.5	70.5
Crosscarmellose sodium	5						
Crospovidone		5			3		2.5
Sodium Starch Glycolate			5				
KyronT-134(Polacrillin Potassium				5		3	2.5
Aerosil200(Colloidal Silicondioxide)	2	2	2	2	2	2	2
Povidone	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1
Sucralose	3	3	3	3	3	3	3
Vanilla flavor	2	2	2	2	2	2	2
Total Weight	100	100	100	100	100	100	100

Procedure for Direct Compression Method[23]

- Accurately weigh Milnacipran Hydrochloride, filler, superdisintegrants,sweetner and flavour.
- Sift all the excipients through ASTM # 40.
- Mix all the excipient with drug and blend the sifted material together for 5 minutes.
- Weigh and sift magnesium stearate through ASTM # 60.
- Lubricate the blend with sifted magnesium stearate for 2 minutes.
- Compress the above blend in CEMACH mini Rotary Tableting Machine using 8mm concave punches, upper punch embossed with “c” with the average weight of 100 mg.

EVALUATION OF TABLETS

1. Post-compression parameter

The tablets were evaluated for in-process and finished product quality control tests i.e., weight Variation, Thickness, Hardness, Friability, Tensile strength, Drug content, *in vitro* dispersion time, Disintegration time, water absorption ratio, wetting time and *in vitro* drug release studies

❖ Weight Variation:[55]

The test ensures that all the tablets in each batch are of same potency, within reasonable limits. According to weight variation test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. then the weights of the individual tablets were compared with the average weight to determine the weight variation.

❖ Tablet Crushing Strength[57]

Crushing strength (Hardness) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablet.

In process tablet crushing strength were measured using Monsanto Hardness Tester.

Post compression tablets of optimized tablets of were evaluated for crushing strength using TA XT plus,Stable Microsystems,UK.The Tablet tensile strength is the force required to break a tablet by compressing it in radial direction.[55]

Preliminary Setting of Texture Analyser

Table.No.7 TA settings and Parameters

Sequence Title	Return to Start
Test Mode	Compression
Pre-test Speed	2.0 mm/sec
Test speed	0.03 mm/sec
Post test speed	10.0 mm/sec
Target mode	Distance

Distance	0.5 mm
Trigger Type	Auto (force)
Trigger Force	100g
Probe	p/25 diameter
Points per second	500

The tablet crushing strength (TCS) was calculated using the formula (as per USP monograph(<1217>).

$$\sigma_X = \frac{10F}{\pi D^2}\left[\frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01\right]^{-1}$$

Where

θ_x is the tensile strength,

F is the breaking force,

D is the tablet diameter,

H is the tablet thickness, and

W is the central cylinder thickness

❖ **Thickness[53]**

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper.It is expressed in millimetre.

❖ **Friability[53]**

Friability test was performed to assess the effect of friction and shock which may often cause tablets to chip,cap or break.. Friability of tablets was determined using Roche Friabilator . 20 tablets were taken in a friabilator and was operated for 100 revolutions in 25 RPM and tablets were weighed again. Tablets should not lose more than 1% of their weight.

❖ **Wetting Time And Water Absorption Ratio[23]**

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs

to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet.

It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity.

Five circular tissue paper were placed in a petric dish with a 10 cm diameter.Ten millilitres of water containing eosin,a water soluable dye was added to the petricdish.The dye solution is used to identify the complete wetting of the tablet surface.A tablet was carefully placed on the surface of tissue paper in the petricdish at room temperature.The time required for water to reach the upper surface and wet the tablets completely wet was noted as the wetting time. The measurements were carried out in replicates.

The same procedure was repeated for determining water absorption ratio.The wetted tablet was then weighed.Water absorption ratio,was determined using the formula.

$$R = (Wa - Wb) / Wa \times 100$$

Wa = Weight of the tablet after wetting

Wb = Weight of the tablet before wetting

- **Drug Content**[53]

20 were weighed and tablets were weighed and titurated.in motor.The tablet triturate equivqlent to 12.5mg of drug was d accurately weighed and diluted in 0.1N Hydrochloric acid .The diluted solutions absorbance was determined by UV spectrophotometer at 223nm aganist the blank. The drug content should be within 90 % to 110% of the labelled claim.

- **Uniformity of dosage forms** [53]

Uniformity of dosage units is defined as the degree of uniformity in the amount of

drug substance in each unit.

As per (USP 30 NF 25) uniformity of dose units was performed.

Table for Application of content uniformity (CU) and weight variation test (WV) for tablet dosage form USP was presented below.

			Dose andRatio of drug substance >25mg & >25 %	Dose and Ratio of drug substance < 25mg & <25 %
TABLETS	Uncoated	-	WV	CU
	Coated	Film coated	WV	CU
		others	CU	CU

Uniformity of Dosage units performed by content uniformity method because percentage of drug is less than 25 mg.

❖ **Content Uniformity**[53]

10 dosage units are weighed and dissolved in 0.1N Hydrochloric acid separately. Diluted solutions are assayed individually and acceptance value is calculated.

Acceptance Value = M -|X| + ks

M – Reference Value

X – Mean of individual contents

K – Acceptability Constant [if n =10 then k =2.4 and if n= 30 then k = 2]

s- Sample Standard deviation.

❖ **Disintegration Time**[53]

The Invitro disintegration time was determined using disintegration test apparatus. Six tablet were placed individually in each test tube of disintegration test apparatus . . The

time taken for each tablet to disintegrate completely was recorded.

❖ ***In-vitro*** **Dispersion Time**

In vitro dispersion time was measured by dropping a tablet in petricdish containing 6 ml of water.Three tablets from each formulation were randomly selected and invitro dispersion time was performed.

❖ ***In-vitro*** **Dissolution Parameters**[48]

As per FDA Dissolution Data base the recommended dissolution medium for Milnacipran Hydrochloride is 0.1N Hydrochloric acid. Hence 0.1N Hydrochloric acid was selected as a medium.

Following conditions were followed to study in-vitro dissolution of formulations.

Dissolution apparatus	: USP – I (Paddle)
Dissolution Medium	: 0.1 N Hydrochloric acid
Volume of dissolution fluid	: 900 ml
Temperature	: 37 ± 0.5°C
RPM	: 50

Samples were withdrawn at 2, 5, 10, 15, 20 and 30 minutes time intervals by replacing with same dissolution medium.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

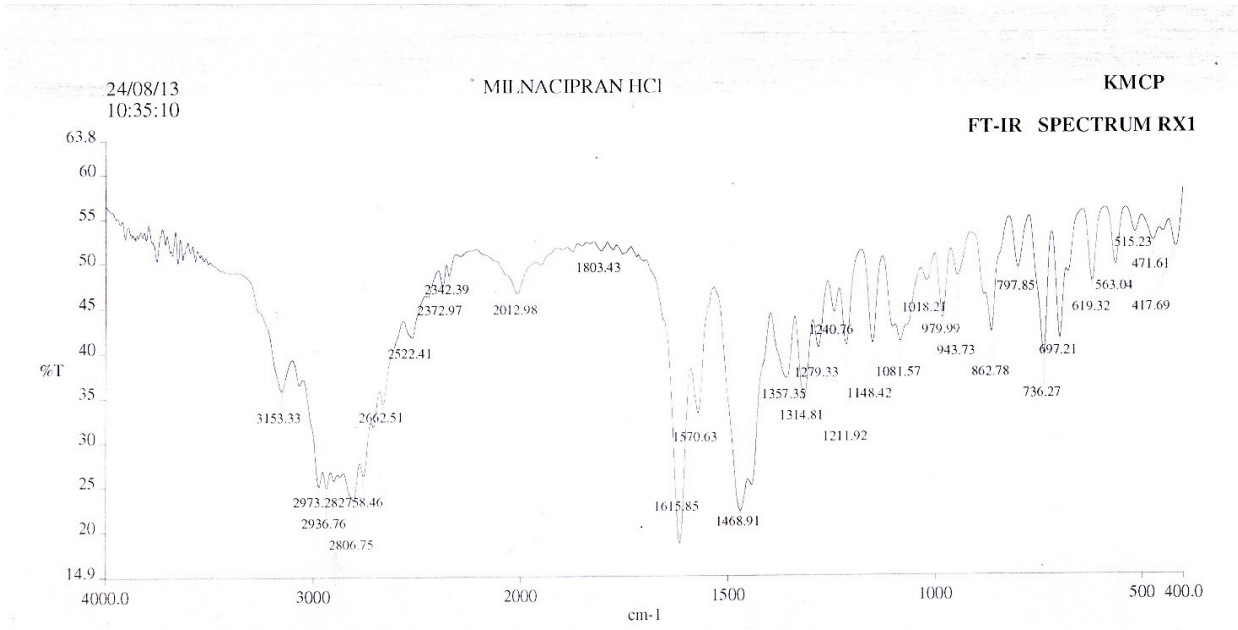
Organoleptic Evaluation

Milnacipran Hydrochloride is white to off white crystalline powder,odourless, and is slightly bitter.Bitter taste were masked by using sweeting agent.

Analytical Evaluation

I.R Spectroscopic Analysis

Fig.No.4 FTIR Spectrum of Milnacipran Hydrochloride



Spectrum Pathname: C:\PEL_DATA\SPECTRA\MILNACIPRAN HCl.002

MILNACIPRAN HCl.pk

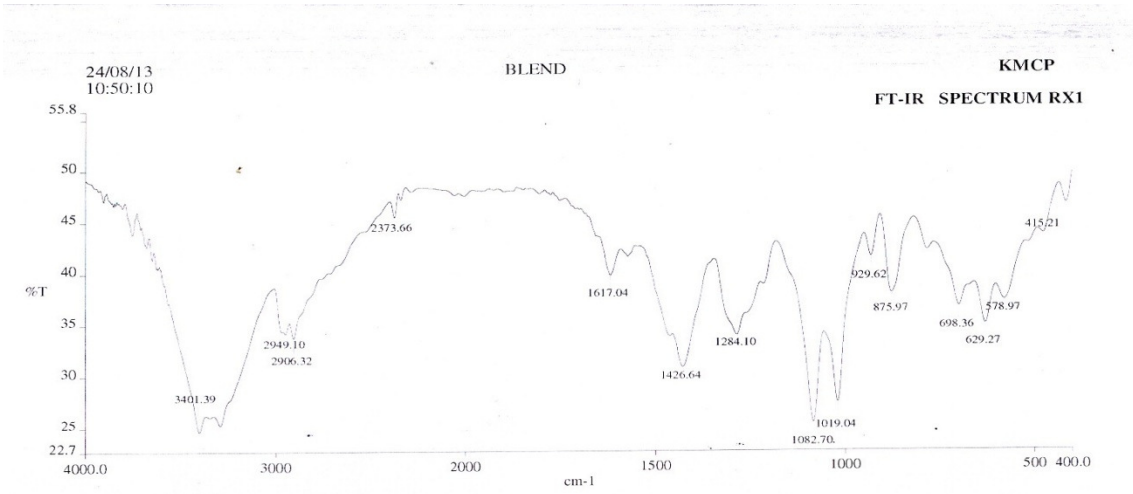
MILNACIPRAN HCl.002 3601 4000.00 400.00 18.49 58.09 4.00 %T 4 1.00

REF 4000 56.51 2000 47.16 600
3905.62 52.72 3855.29 52.59 3754.19 50.30 3680.06 50.93 3653.13 50.00
3630.44 50.45 3569.68 50.27 3153.33 35.74 2973.28 25.02 2936.76 24.93
2806.75 23.46 2758.46 26.16 2662.51 34.25 2522.41 41.64 2372.97 47.32
2342.39 48.47 2012.98 46.48 1803.43 51.19 1615.85 18.49 1570.63 33.13
1468.91 22.16 1357.35 36.94 1314.81 34.63 1279.33 40.40 1240.76 44.31

Table .no.8 IR Spectral Data for Milnacipran Hydrochloride

S.No	Wave Number in Cm^{-1}	Group Assigned
1.	2973.28	C-H-Streching
2.	1615.85	C=0 Streching
3.	1570.63	C=C Streching
4.	1240.76	C-N Streching
5.	862.78	C-H Deformation

Fig.no 5 FTIR Spectrum for Blend



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BLEND.pk

BLEND.002 3601 4000.00 400.00 24.60 49.54 4.00 %T 4 1.00

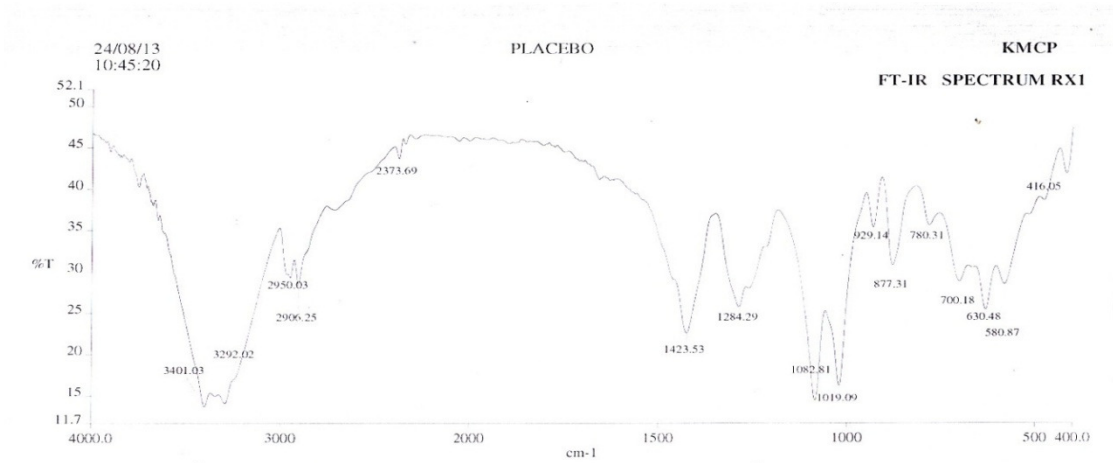
REF 4000 49.13 2000 47.49 600
3757.93 43.80 3401.39 24.60 2949.10 34.17 2906.32 33.75 2373.66 45.39
1617.04 39.74 1426.64 30.84 1284.10 33.94 1082.70 25.43 1019.04 27.39
929.62 41.49 875.97 37.96 698.36 36.67 629.27 34.98 578.97 37.26
415.21 46.59

Table.No.9 IR Spectral Data for Blend

S.No	Wave Number in Cm^{-1}	Group Assigned
1.	3401.03	O-H-Streching
2.	3292.02	N-H Streching

3.	2950.03	C-H Streching
4.	877.31	C-H Deformation
5.	1019.09	C-O Streching
6.	1284.29	C-N Streching
7.	1725.17	C-O Streching
8.	1423.53	C=C Streching
9.	1082.81	C-O-C Streching
10.	780.31	C-CL Streching

Fig no.6 FTIR Spectrum of Placebo



Spectrum Pathname: C:\pel_data\spectra\PLACEBO.002

PLACEBO.pk

PLACEBO.002 3601 4000.00 400.00 13.68 47.32 4.00 %T 4 1.00

REF 4000 46.75 2000 45.81 600
3753.21 40.26 3401.03 13.68 3292.02 14.05 2950.03 29.30 2906.25 28.59
2373.69 43.65 1423.53 22.59 1284.29 25.75 1082.81 14.37 1019.09 16.22
929.14 35.33 877.31 30.77 780.31 35.56 700.18 28.82 630.48 25.43
580.87 28.50 416.05 41.80

Table.no.10.IR Spectral Data of Placebo

S.No	Wave Number in Cm^{-1}	Group Assigned
1.	3401.39	O-H-Streching
2.	2949.10	C-H Streching
3.	1617.64	C=O Streching
4.	1426.64	C=C Streching
5.	1284.10	C-N Streching

6.	1082.81	C-O-C Streching
7.	1019.09	C-O Streching
8.	698.36	C-Cl Streching
9.	875.97	C-H Deformation

DISCUSSION

Results indicates that,there is no interaction between Milnacipran Hydrochloride and excipients used in the formulation.

PREPARATION OF STANDARD CURVE OF MILNACIPRAN HYDROCHLORIDE

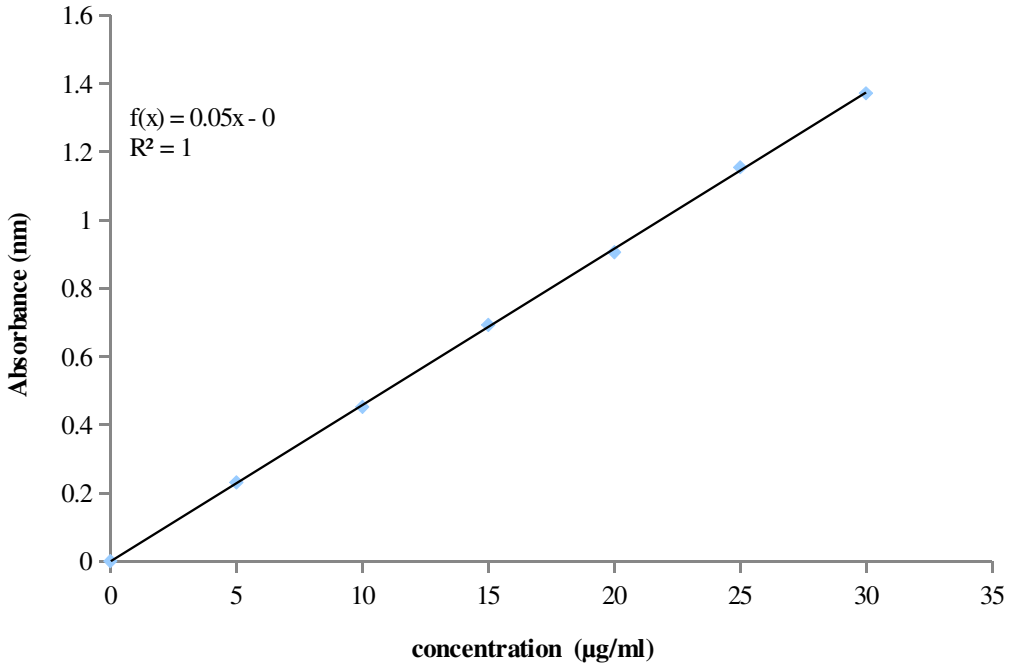
The Absorbance of Milnacipran Hydrochloride with different concentrations in 0.1 N Hydrochloric acid were tabulated below

Table.No.11 Standard Curve of Milnacipran Hydrochloride

Concentration (µg/ml)	Absorbance
5	0.231
10	0.452

15	0.692
20	0.905
25	1.154
30	1.371

Fig no.7 CONCENTRATION Vs ABSORBANCE



BULK CHARACTERISATION

Evaluation of Milnacipran Hydrochloride

The powder was evaluated for Bulk density, Tapped Density, Compressibility index and Hausner's ratio.

Table.No.12 Evaluation of Pure Drug

Sample	**Bulk Density (gm/ml)**	**Tapped Density (gm/ml)**	**Percentage Compressibility (Carr's index)**	**Hausner's ratio**	**Angle of Repose ()**
Pure Drug	0.491 ± 002	0.621 ± 0.03	18.28 ± 0.04	1.166 ± 0.03	$31^0$12'± 0.31

Discussion

The above result indicate that the Milnacipran Hydrochloride is having good compressibility due to its crystalline structure.Angle of repose of drug was found to be in the range of Passable (as per USP), which may due to its irregular partical size and particle size distribution.

FORMULATION DEVELOPMENT

Formulation development of Milnacipran Hydrochloride was performed by direct compression

The Physical Characteristics of the prepared blend was performed and the results were given below

Table.NO.13 Evaluation of Directly Compressible Blend

Sl.no	Parameters	F1	F2	F3	F4	F5	F6	F7
1	Bulk Density (g/ml)	0.412 ± 0.02	0.401 ± 0.03	0.406 ± 0.04	0.423 ± 0.02	0.414 ± 0.02	0.409 ± 0.03	0.427 ± 0.02
2	Tapped Density (g/ml)	0.471 ± 0.03	0.455 ± 0.02	0.453 ± 0.03	0.482 ± 0.02	0.471 ± 0.03	0.458 ± 0.02	0.489 ± 0.02
3	Compressibility index (%)	12.4	11.88	10.37	12.2	12.10	10.69	12.67
4	Hausner's Ratio	1.14	1.13	1.11	1.13	1.13	1.11	1.14
5	Angle of repose	30^0 33'	26^0 29'	29^0 67'	27^0 45'	28^0 34'	29 ^{0}23'	$28^0$89'

Discussion

From the obtained results it was found that all the batches have good flow property and compressability. as per USP specifications.

SELECTION OF DISINTEGRANT

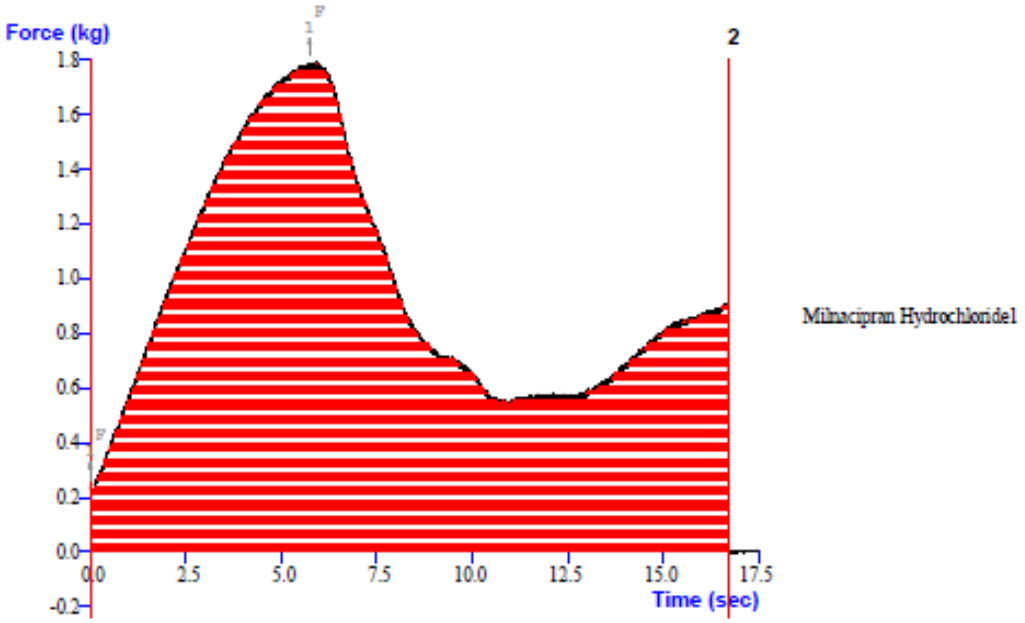
To select a disintegrants batch with Crospovidone,Kyron,T-314,Croscarmellose sodium.,Sodium starch Glycolate with maximum concentration were taken and it is checked for the physio chemical properties of the tablet. Among the batches taken the tablets with Sodium Starch Glycolate as a disintegrants shows maximum dispersion time. Sodiumstarch Glycolate is having 2 minute 15 seconds and Croscarmellose sodium is having 1 minute 36 seconds were as, kyron T-314 and Crospovidone shown dispersion time of 24 seconds and 26 seconds respectively.Hence Crospovidone and Kyron T-314 were selected for further trials .

Batches with 3 % of Crospovidone and 3 % Kyron T-314 was taken and it shown that dispersion time was more than 30 seconds. Hence to reduce the dispersion time batch with Kyron T-314 and Crospovidone of 2.5 % each were taken .It was observed that it is showing dispersion time of 21 second.To optimise the final formula dissolution studies were performed on batchs with 5%Kyron T-314, 5% Crospovidone,and batchs with disintegration combination (2.5% each) of Kyron T-314 and Crospovidone.

Table.No.14 Evaluation of optimized formulations of F2, F4 and F7

Evaluation Parameters	**F2**	**F4**	**F7**
Weight Variation (mg)	99.56 ± 0.3	100.08 ± 0.5	99.65 ± 0.6
Thickness (mm)	2.13 ± 0.3	2.11 ± 0.3	2.10 ± 0.2
Inprocess Crushing Strength by Monsanto Hardness Tester(kg/cm^2)	1.75 ± 0.3	1.80 ± 0.4	1.85 ± 0.4
Friability (%)	0.36 ± 0.05	0.38 ± 0.07	0.35 ± 0.02
Disintegration Time (sec)	20	18	16
Dispersion Time (sec)	26	24	21
Wetting Time (sec)	23 ± 1.22	24 ± 1.53	19 ± 1.26
Water Absorption Ratio (%)	65 ± 0.53	67 ± 0.25	62 ± 0.87
Drug Content	99.6 ± 1.57	99.9 ± 1.65	100.1 ± 1.48
Content Uniformity (L_1 Value)	1.72	1.69	1.54
Tablet Crushing Strength by TA XT Plus Analyser(N/mm^2)	1.08 ± 0.6	1.02 ± 0.6	1.12 ± 0.06

Fig.no.8 Texture Analysis by TA XT Plus Analyser



Discussion

The percentage weight variations for all batches were found to be within the Pharmacopeial limit. All the batches showed weight uniformity

The crushing strength of all batches was almost uniform and possess good mechanical strength with sufficient hardness.

The percentage friability of all batches was below 1% indicating that all formulation possess good mechanical strength.

The disintegration time of all the batches were found to be almost less than 30 sec

The drug content and the uniformity of dosage forms of all the three batches was found within the limits as per US pharmacopeia

INVITRO DISSOLUTION STUDIES OF OPTIMIZED FORMULATIONS

Table.No.15 IN VITRO DISSOLUTION STUDY OF BATCH F2

Time (min)	Cumulative % drug Release
2	46.18
5	70.8
10	75.3
15	80.4
20	85.6
25	90.2
30	95.6

Fig.no.9 Time Vs Cumulative % drug release

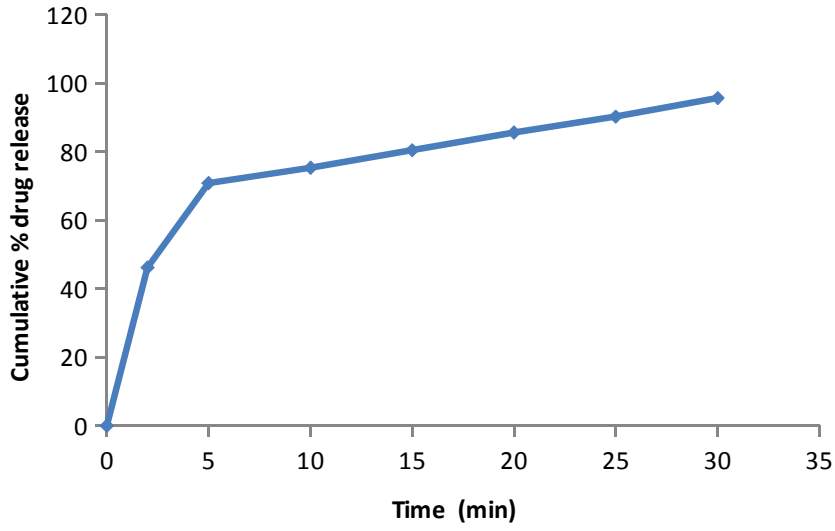


Table.No.16 INVITRO DISSOLUTION STUDY OF BATCH F4

Time (min)	Cumulative % drug Release
2	48.62
5	70.3
10	78.6
15	83.9
20	88.5
25	92.5
30	97.3

Fig.no.10 Time Vs Cumulative % of drug

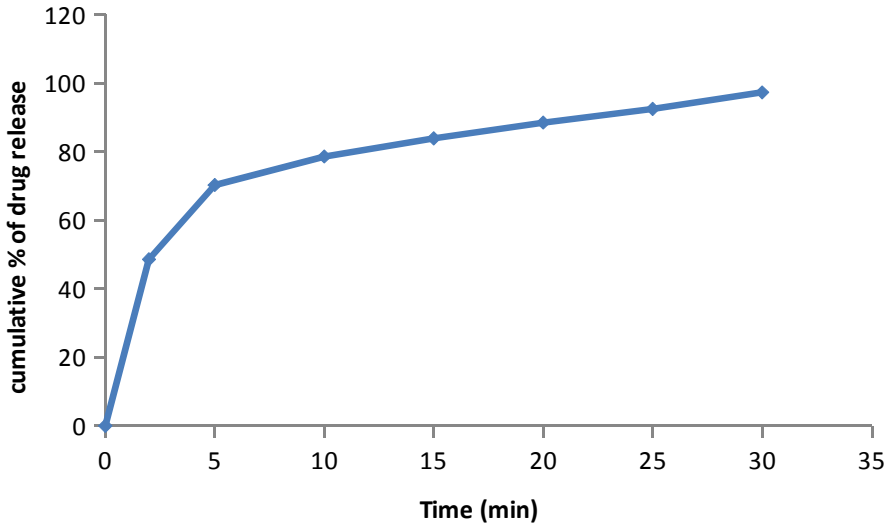


Table .No.17 INVITRO DISSOLUTION STUDY OF BATCH F7

Time (min)	Cumulative % drug Release
2	70.2
5	86.7
10	94.4
15	95.3
20	97.4
25	98.6
30	99.8

Fig.no.11 Time Vs Cumulative % of drug

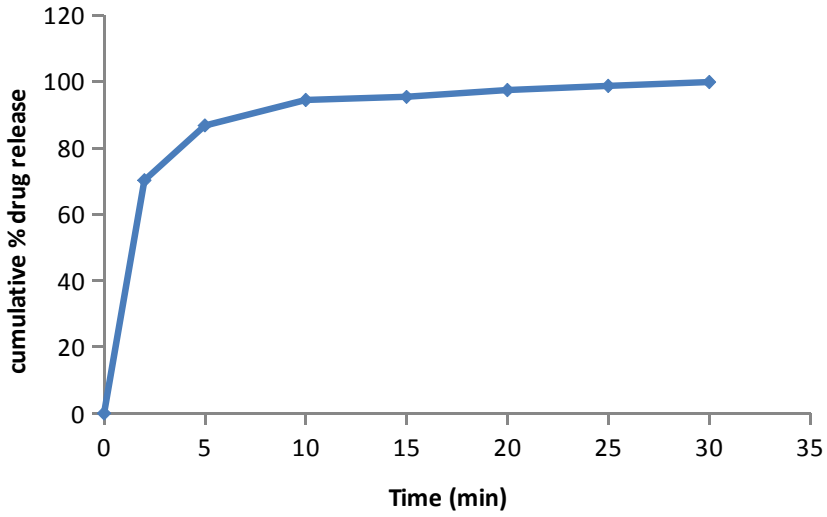
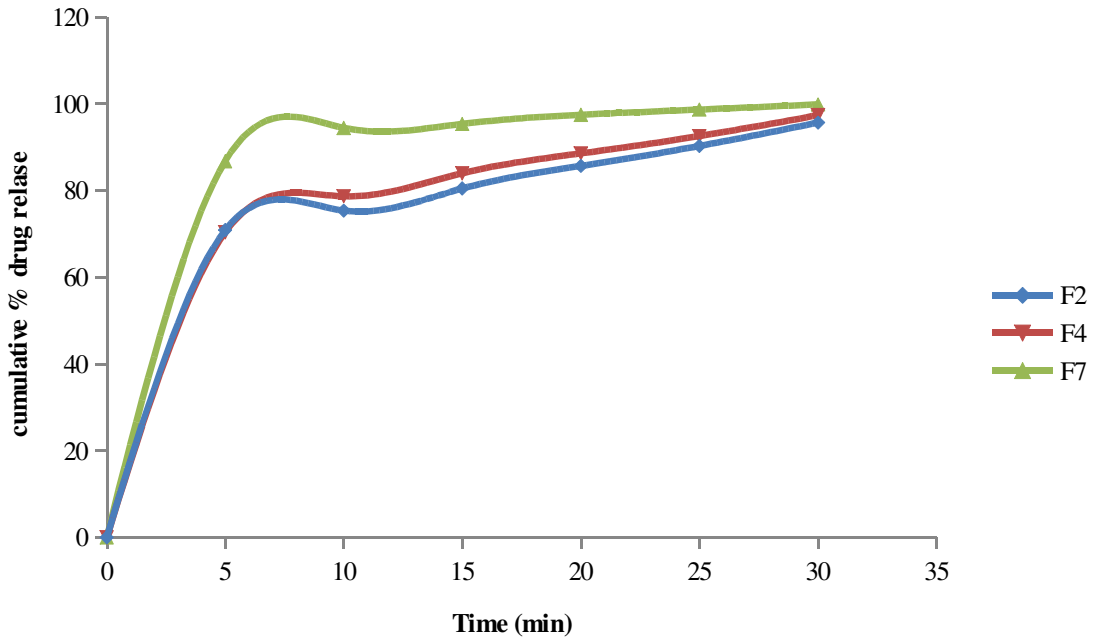


Fig.no.12 Comparative dissolution Profile of F2,F4 and F7 batches



Discussion

Comparative dissolution data shows that batch with Kyron T-314 and crospovidone (2.5% each) is giving better dissolution rate compared to other two batches. Hence the formula was considered as the finalized formula.

SUMMARY

Oro dispersible tablets of Milnacipran Hydrochloride is an anti depressant drug which is highly appropriate as it has ease of administration for the patients having major depressive disorder.

Orodispersible tablets (ODT) have better patient acceptance and compliance ,may offer improved patient compliance compared with conventional oral dosage forms as the drug dissolves in saliva within a matter of seconds.

Literature regarding drug, excipients selection, manufacturing method, etc, has been collected and reviewed. Analytical method was developed for Milnacipran Hydrochloride using UV-spectrophotometer at 223nm.It obeys beer-lamberts law between 4-40 g/ml.

FTIR study of the pure drug and Final Lubricated blend was performed and result confirms that the drug is compatabile with other excipents.

Pre-compression parameters such as bulk density tapped density, compressibility index, hausner's ratio and angle of repose were performed and results indicate that all the final lubricated blends are having good flow property.

Initial trials with Sodium Starch Glycolate ,Crospovidone, Crosscarmelose sodium and Kyron T-314 were taken with 5%of superdisintegrant. Among these batches taken,kyron T-314 and crospovidone shows better dispersion time within 30 seconds compared to the other two superdisintegrants.

To optimize the concentration of superdisintegrant batches with 5% of crospovidone, 5% kyron T-314 and batch with 2.5% of crospovidone and 2.5 % of kyron T-314 were taken .Dispersion Time of batches mentioned are sec,26 sec and 20 seconds respectively.

Post compression parameters such as weight variation, hardness, thickness, friability and drug content,uniformity of dosage forms were performed and tablets of these formulation were found to be within the limits. To select a final formula,dissolution profiling of all the three batches were performed and found that batch

with kyron T-134 and crospovidone (2.5% each) given better rate of dissolution than other two batches.Hence the batches with both disintegrant was selected as a final formula.

Here, the vital rationale of developing the oral disintegrating tablet was achieved. Formulation F7 showed the disintegration within 20 sec and the dispersion time at 21 sec by using the combination of crospovidone and Kyron T-314 as a superdisintegrants. as the concentration increases.dispersion time also get decreases..

CONCLUSION

The formulation of oro dispersible tablets of Milnacipran hydrochloride complines all the requirements of mouth dissolving tablet .

From the results of the study we conclude that formula F7 (mannitol crospovidone,Kyron T-314,povidone ,magnesium stearate ,sucralose,Vanilla) processes good disintegration and dissolution profile with the addition of superdisintegrants.On comparing all the batches, F7 passess all the quality control tests

Milnacipran Hydrochloride is not avaliabe as a patient compliance orally disintegrating tablet dosage form in market.Hence by preparing Orally disintegrating tablet of Milnacipran hydrochloride ,the fulfilment and speedy recovery of patients is possible in future.

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